REMARKS

AMENDMENTS TO THE SPECIFICATION

The Title of the specification was amended to delete "CLONING AND EXPRESSION", and to append "POLYNUCLEOTIDES ENCODING". These amendments were made solely to address the Examiners objection to the same in an effort to more clearly indicate the invention to which the claims are directed. Support for these amendments may be found in paragraph 12, original Claim 1, and pending Claims 21-40. No new matter has been added.

Paragraph 88 was amended to append both the date ("November 20th, 2001") and the deposit number ("PTA-3873") for the hSLAP-2 clone. Applicants respectfully point out to the Examiner that the date of deposit assigned to the hSLAP-2 clone on the official ATCC Deposit Form (submitted herewith), November 20th, 2001, is the same day as the official filing date of the present application, November 20th, 2001. The hSLAP-2 clone is specifically referenced on the ATCC Deposit Form (referenced as "hSLAP-2" in the "Identification Reference by Depositor" section). In accordance with 37 CFR 1.804 (MPEP 2406.01), and in view of In re Lundak, 773 F.2d 1216 227 USPQ 90 (Fed. Cir. 1985), Applicants believe no new matter has been added.

STATUS OF THE CLAIMS:

Claims 1 to 20, 26 to 30, 32, and 38 to 40 are cancelled.

Claim 21 was amended.

New Claims 41 to 44 were added.

Claims 21 to 25, 31, 33 to 38, and 41 to 44 are pending.

Claim 21 was amended to delete Claim 21(c), (d), (e), (f), and (h). Applicants assert that this amendment was not made to overcome any issues related to the patentability of this claim. Applicants reserve the right to prosecute Claims 21(c), (d), (e), (f), and (h) as originally presented in related applications. Applicants right to equivalents of Claim 21 is reserved.

Claim 21 was also amended to delete the "or fragment thereof" limitation of Claim 21(g). Support for this amendment may be found in paragraph numbers 118, 133-146, and throughout the specification as originally filed. Applicants reserve the right to prosecute Claim 21(g) as originally presented in related applications. Applicants right to equivalents of Claim 21 is reserved. No new matter has been added.

Claim 21 was further amended to delete "(c), (d), (e), (f)" from Claim 21(g) to reflect the amendment to delete Claims 21(c), (d), (e), and (f) above. Claim 21 was further amended to change the location of the "and" from being located after Claim 21(g) to being located after Claim 21(b) to reflect the amendment to delete Claims 21(c), (d), (e), (f), and (h) above and to ensure Claim 21 continues to maintain proper Markush form. Claim 21(g) was amended to append "or" in between "(a)" and "(b)" to reflect the amendment to delete Claims 21(c), (d), (e), and (f) above. Applicants assert that these amendments were not made to overcome any issues related to the patentability of this claim and that Applicants right to equivalents of Claim 21 is reserved.

Claim 25 was amended to correct a typographical error that incorrectly listed the coding region for the polypeptide specified in Claim 21(b). Claim 25 was amended to change "517 to 684" to "418 to 1197". Support for this amendment may be found in original Claims 21 and 23, and Figures 3A-B. Applicants assert that this amendment was not made to overcome any issues related to the patentability of this claim and that Applicants right to equivalents of Claim 25 is reserved. No new matter has been added.

Claims 26 to 30, 32, and 38 to 40 have been cancelled. Applicants reserve the right to prosecute Claims 26 to 30, 32, and 38 to 40 in related applications.

New Claims 41, 42, 43, and 44 were added. Support for new Claims 41, 42, 43, and 44 may be found in original Claim 21(c) and (d), original Claim 27, Example 1, and Figures 3A-B. No new matter has been added.

I. Miscellaneous

a. Public Access to ATCC Deposit No. PTA-3873

Applicants representative hereby gives the following assurance by signature below:

Bristol-Myers Squibb Company, an assignee of the present application, has deposited biological material under the terms of the Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for the Purposes of Patent Procedure with the following International Depository Authority: American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209. This deposit comprises the cDNA sequence encoding the hSLAP2 polypeptide of the present invention. The deposit for hSLAP2 was made on November 20th, 2001, and given ATCC Accession Number PTA-3873. In accordance with MPEP 2410.01 and 37 C.F.R. § 1.808, assurance is hereby given that all restrictions on the availability to the public of ATCC Accession Number PTA-3873 will be irrevocably removed upon the grant of a patent based on the captioned application, except as permitted under 37 C.F.R. § 1.808(b).

A copy of the ATCC Deposit receipt for Accession Number PTA-3873 is enclosed herewith.

II. Objections to the Specification

a. Title

The Examiner has objected to Applicants Title of the specification requesting a new title "that is clearly indicative of the invention to which the claims are directed". In response, Applicants have amended the Title to delete "CLONING AND EXPRESSION", and to append "POLYNUCLEOTIDES ENCODING". Applicants believe the Title is now consonant with the pending claims and that the Examiners objection has been overcome in consideration of Applicants amendments.

b. Specification

The Examiner has objected to Applicants paragraph 88, page 24 as missing the "Deposit and ATCC Accession Number for [the] hSLAP2 cDNA". In response, Applicants have amended paragraph 88 to append "November 20th, 2001" and "PTA-3873", which represent the date and deposit number, respectively, for the hSLAP clone. In accordance with 37 CFR 1.804 (MPEP 2406.01), and in view of In re Lundak, 773 F.2d 1216 227 USPQ 90 (Fed. Cir. 1985), Applicants

believe no new matter has been added. Applicants believe the Examiner's objection to the same has been overcome in consideration of Applicants amendments.

III. Rejections under 35 U.S.C. § 101

a. The Examiner has rejected 21 to 40 under 35 U.S.C. § 101, for failure to demonstrate a specific and substantial asserted utility or a well-established utility. More particularly, the Examiner alleges that "[t]he specification fails to provide sufficient objective evidence of any activity for encoded protein. Applicant only states that said protein shows 47 % identity to human SLAP and 58 % identity to the mouse SLAP proteins (see Table 4 and page 61, lines 22-30 in particular). The specification disclosed that based on sequence homology to related molecules, said protein may be a novel human SLAP-2 protein. The specification also disclosed that said hSLAP-2 nucleic acid sequence and related protein can be used for diagnosing, treating or preventing disorders or diseases associated with aberrant or uncontrolled cellular signal transduction or with hyperactive cell, or may play a role in one or more aspects of regulating the immune system and tumor cell biology (see page 20, lines 5-20 and page 41, lines 22-30 in particular). No well-established utility for a human SLAP-2 protein is indicated".

Applicants disagree. In response to the Examiners allegation that the instant disclosure does provide sufficient objective evidence of any activity for the encoded protein, Applicants wish to point out to the Examiner that the patent laws do not require that a specification actually demonstrate use of a claimed invention. Rather, it is established law that a disclosure is enabling so long as it contains information which would lead one of ordinary skill in the art to *reasonably believe* the claimed invention has utility. *In re Barr*, 170 U.S.P.Q. 330 (C.C.P.A. 1971). In the absence of evidence or apparent reason why the claimed polynucleotides do not possess the disclosed utility, the allegation of utility in the specification *must* be accepted as correct. *Ex parte Krenzer*, 199 U.S.P.Q. 227 (Pat. Off. Bd. App. 1978). Applicants assert that one skilled in the art would reasonably believe that hSLAP-2 is a new member of the SLAP family of adapter proteins based upon the evidence provided in the instant specification and would have the utilities asserted by Applicants specification.

Specifically, Applicants specification teaches that the hSLAP-2 polypeptide is an adaptor protein which functions "in the receptor-ligand signal transduction pathway in cells of the hematopoietic lineage" (see paragraph 54). More particularly, Applicants specification teaches that

hSLAP-2 is a "negative regulator[s] of intracellular signal transduction in several cell types, including T-cells" (see paragraph 76). Applicants specification also teaches that hSLAP-2 is useful for "the diagnosis, screening, monitoring, therapy, and prevention of immune system related conditions or diseases, particularly those involving T-cell and B-cell neoplasms; inflammation disorders, diseases and conditions, rheumatoid arthritis, osteoarthritis, psoriasis, rhinitis, inflammatory bowel disease (Crohn's and ulcerative colitis), allergies, particularly those involving hyperactivity of B-cells and T-cells, or other immune cells, such as mast cells or eosinophils; autoimmune diseases such as systemic lupus erythematosus and multiple sclerosis; pulmonary diseases including asthma, acute respiratory distress syndrome, and chronic obstructive pulmonary disorder; tissue/ organ rejection; and cancer" (see paragraph 12).

As appreciated by the Examiner, Applicants specification also teaches that hSLAP-2 shares significant identity to the human and mouse SLAP proteins, sharing 47.4% and 58.1% identity, respectively (see paragraph 210 and Figure 4). Importantly, Applicants specification provides detailed teachings that show both the presence and location of domains that are characteristic of Src-like adaptor family members, such as the presence of the SH3 domain (residues 35 to 90 of SEQ ID NO:2) and an SH2/ SH3 domain (residues 94 to 176 of SEQ ID NO:2) (see paragraph 210). The presence of these domains alone is sufficient evidence to demonstrate that hSLAP-2 is an adaptor protein (see entire article of Pawson T. et al, Science, 278:2075-2080 (1997); submitted concurrently herewith), and the homology to SLAP in conjunction with the presence of these domains is sufficient evidence to demonstrate that hSLAP-2 is a Src-like adaptor family member (see Results and Discussion section of Pandey, A., et al., J. Biol. Chem., 270:19201-19204 (1995); submitted concurrently herewith.

Applicants specification also teaches that hSLAP2 shares significant homology to the SH2/ SH3/ SH3 domains of the Lyn and Hck tyrosine kinases from the Src-family (see paragraph 210). The structural conservation of the SH2 and SH2/SH3 domains of hSLAP2 to other immune adaptor proteins is significant based upon the appreciation in the art that distinct signaling cascades required for lymphocyte activation depend upon the involvement of specific adaptor proteins (see entire articles of Kelly et al., Curr. Opin. Immunol., 12:267-275 (2000); Tomlinson et al., Immunol. Today 21:584-591 (2000); Myung et al., Curr. Opin. Immunol., 12:256-266 (2000); and Kurosaki, T. et al., Ann. Rev. Immunol., 17:555-592 (1999); submitted concurrently herewith). Thus, one skilled in the art would only need to appreciate which adaptor protein a particular protein is most homologous to in order to associate it with a specific signaling cascade required for lymphocyte activation. Once a

signaling cascade is identified, the utility of such a protein would be implicit with the signaling cascade. The homology to Lyn and Hck within the SH2 and SH2/SH3 domains clearly places hSLAP-2 within the Src signaling cascade, while its overall homology to SLAP clearly associates hSLAP-2 with being a member of the Src-like adaptor protein (SLAP) family.

Applicants specification also teaches that like human SLAP, hSLAP-2 has a restricted expression pattern being primarily expressed in "immune system cells includ[ed]ing peripheral blood lymphocytes, Jurkat T-cells and bone-marrow cells" (see paragraph 211). The asserted utility of hSLAP-2 as representing a new member of the SLAP family of adaptor proteins is based upon the significant structural and sequence homology to the human and mouse SLAP proteins, the presence of conserved domains essential for SLAP family function, in addition to its shared expression pattern to SLAP.

Applicants assert that one skilled in the art would have readily appreciated that hSLAP-2 is a member of the SLAP family based upon the totality of the evidence provided in Applicants specification as originally filed, and that hSLAP-2 would have a similar utility as the established utility of SLAP as asserted by Applicants specification. Specifically, Applicants assert that one skilled in the art would have appreciated that hSLAP-2 would be useful as a negative regulator of intracellular signal transduction in immune cell types, including T-cells and B-cells, and would be useful as a target for therapeutic intervention of disorders related to aberrant T-cell and B-cell activation based upon the teachings of Applicants specification.

Applicants assert that these utilities are "specific" since they are specific to immune disorders, and not just any disorder. Applicants also assert that these utilities are "substantial" since disorders afflicting aberrant B-cell and T-cell receptor activation represent a significant source of mortality and disease in humans in the world today. Applicants believe the claimed hSLAP-2 polynucleotide has a substantial utility and does not represent a throw-away utility. Applicants assertion is exemplified by the fact that unregulated cellular proliferation and uncontrolled clonal expansion in B-cells can result in B-cell tumors, lymphomas and leukemias. In addition, unregulated activation of B-cells may also contribute to a variety of autoimmune diseases mediated by self-reactive antibodies. Applicants assertions are further exemplified by the fact that unregulated activation of the T-cell receptor (TCR) can lead to aberrant T-cell growth, resulting in, for example, T-cell tumors, lymphomas, leukemias and thymomas.

In addition to a specific and substantial utility, as Applicants have asserted, the Revised Utility Examination Guidelines require that such utility be credible (a "credible utility"). That is,

whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. Such assertions are credible unless "(A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion." See, Revised Utility Guidelines Training Materials. Applicants believe that one skilled in the art of immunology, upon reviewing the totality of the evidence taught by Applicants specification, would logically arrive at the same conclusion as Applicants that hSLAP-2 is a Src-like adaptor protein family member and would have the utilities asserted by Applicants. Because Applicants have asserted specific and substantial utilities that are credible, Applicants have also complied with the credible utility requirement.

Further, PTO personnel are reminded that they must treat as true a statement of fact made by Applicants in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. Significantly, no such countervailing evidence has been provided. If such evidence is available to the examiner, Applicants request that the Examiner provide an affidavit pursuant to 37 C.F.R. § 1.104(d)(2) containing evidence substantiating this position.

The Examiner also alleges that Applicants specification contains "no information pertaining to the significance of the percentage homology, e.g., whether there were any conserved motifs that would led the artisan to accept the protein's function". Applicants disagree and point out to the Examiner that Applicants specification does exemplify the significance of the homology between hSLAP-2 and the human and mouse SLAP proteins as evidenced by Applicants naming of hSLAP-2 (Human Src-Like Adapter Protein-2) after SLAP (Src-Like Adapter Protein). Clearly, the hSLAP-2 nomenclature was not chosen arbitrarily, but rather to specifically recognize its significant structural and sequence homology to, in addition to its shared expression pattern, with SLAP. Contrary to the Examiners allegations, Applicants specification also specifically provides detailed teachings that show both the presence and location of domains that are characteristic of Src-like adaptor family members, such as the presence of the SH3 domain (residues 35 to 90 of SEQ ID NO:2) and an SH2/ SH3 domain (residues 94 to 176 of SEQ ID NO:2) as described above.

The Examiner also alleges that "neither the specification nor the prior art disclose any information regarding the evolutionary significance of this homology or relative conservation of structure and function across species. For example, there is no evidence of record showing why homology to a mouse SLAP would provide a better basis for assigning protein function than homology to a human SLAP."

Applicants point out to the Examiner that Applicants stated homology of hSLAP-2 to the human and mouse SLAP proteins should not be viewed in isolation, but rather should be viewed as collective evidence that hSLAP-2 is closely related to both the human SLAP and mouse SLAP. Applicants specification does not teach that the homology to the mouse SLAP protein is more or less significant than the homology to the human SLAP protein. While it is acknowledged that the hSLAP-2 shares higher identity to the mouse SLAP protein than the human SLAP protein (58.1% identity vs. 47.4% identity), Applicants did not attribute any additional reliance on that result in assigning the function of the hSLAP-2 protein since both the mouse SLAP and human SLAP are orthologs of the same gene. Moreover, Applicants point out to the Examiner that there is no requirement to provide an evolutionary perspective on the observed homology between hSLAP-2 and the mouse and human SLAP proteins. Rather, Applicants assert that one skilled in the art would acknowledge that it is sufficient to provide the percent identity and similarity between the hSLAP-2 and the mouse or human SLAP proteins, or both, in addition to the structural conservation in the SH2 and SH2/SH3 domains, and the immune restricted expression pattern, to demonstrate that hSLAP-2 is a Src-like adaptor protein family member.

Applicants also wish to point out to the Examiner that the Utility requirement may be met by disclosure of a well-established utility for the claimed invention. A well-established utility is defined as a "specific utility" which is well-known, immediately apparent and implied by the specification based on the disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art (Revised Utility Examination Guidelines). Applicants have already asserted *supra* that hSLAP-2 has a specific asserted utility (e.g., useful for negative regulation of intracellular signal transduction, particularly T-cell activation, in several cell types, including T-cells and B-cells, etc.) due to its significant homology to known adaptor proteins, particularly SLAP family members, the presence of the conserved SH2 and SH2/SH3 domains, and the shared expression profile to other SLAP family members. In addition, Applicants have also asserted *supra* that one skilled in the art would readily appreciate this utility based upon the teachings of Applicants specification. Applicants assert that the utility requirement for the claimed invention has been met.

As additional proof that one skilled in the art would readily appreciate Applicants asserted utilities for hSLAP-2 as representing a "well-established" utility, Applicants wish to point out to the Examiner the teachings of Holland et al (J. Exp. Med., 194(9):1263-1276 (2001); submitted

concurrently herewith), Pandey et al (J. Biol. Chem., 277(21):19131-19138 (2002); submitted concurrently herewith), and Loreto et al (Mol. Cell. Biol., 22(12):4241-4255 (2002).

Holland et al describe a protein named SLAP-2 that is 100% identical to hSLAP-2 (SEQ ID NO:2) of the instant specification. Holland et al teach that SLAP-2 is a "novel adaptor protein" that "shares sequence similarity with the known Src-like adaptor protein, SLAP", and that SLAP-2 represents a "novel therapeutic target[s] for autoimmunity and transplant rejection". Holland et al also teaches that SLAP-2 is "predominately expressed in hematopoietic cells", specifically in peripheral blood leukocytes, spleen, thymus, and lung, and that "overexpression of SLAP-2 in B and T-cell lines specifically impared antigen receptor-mediated signaling events". Holland et al appreciated that SLAP-2 contained both SH2 and SH3 Src homology domains and demonstrated that SLAP-2 associates with tyrosine phosphorylated proteins upon antigen stimulation which is consistent with it having a functional SH2 domain.

Similar to the teachings of Applicants specification, Holland et al appreciated the homology of hSLAP-2 to the Src-like adaptor protein, SLAP, in addition to its immune/hematopoietic restricted expression pattern.

Applicants also point out to the Examiner that the instant specification specifically teaches that hSLAP-2 (SEQ ID NO:2) of the present invention is capable of negatively modulating both T-cell and B-cell antigen receptor signaling events (see paragraph 76, 81, and 147), in addition to teaching that hSLAP-2 is useful as a target for therapeutic intervention of autoimmune disorders and organ rejection (see paragraph 12). Importantly, Holland et al also appreciated the utility of hSLAP-2 as representing a novel therapeutic target for autoimmunity and transplant rejection.

Pandey et al also describe a protein named SLAP-2 that is 100% identical to hSLAP-2 (SEQ ID NO:2) of the instant specification. Like Holland et al, Pandey et al teach that SLAP-2 is a "novel adaptor protein containing Src homology 2 and Src homology 3 domains", is "related to a previously identified protein Src-like adaptor protein (SLAP)", and is "predominately expressed in the immune system". Pandey et al also teach that overexpression of SLAP-2 in Jurkat T cells results in the negative regulation of T-cell receptor signaling, and that mutation of the SH2 domain of SLAP-2 abrogates the inhibitory effect. Importantly, Pandey et al also teaches that SLAP-2 interacts with ZAP-70 upon T-cell receptor activation. Applicants specification specifically teaches that hSLAP-2 is capable of binding to ZAP-70 (see paragraphs 149, 152, and 159).

Loreto et al also describe a protein named SLAP-2 that is 100% identical to hSLAP-2 (SEQ ID NO:2) of the instant specification. Like Holland et al and Pandey et al, Loreto et al teach that

SLAP-2 is a "hematopoiesis-specific adaptor protein", "most closely related to SLAP", that contains "a Src homology 3 (SH3) domain and an SH2 domain". Loreto et al also teaches that overexpression of SLAP-2 in Jurkat T cells leads to "inhibition of T-cell antigen receptor-induced activation of nuclear factor of activated cells". Importantly, like Pandey et al, Loreto also teaches that SLAP-2 binds with the phosphoprotein ZAP-70 following stimulation of thymocytes. As discussed *supra*, Applicants specification teaches that hSLAP-2 is capable of binding to ZAP-70 (see paragraphs 149, 152, and 159).

The teachings of Holland et al, Pandey et al, and Loreto et al are directly analogous to the teachings of Applicants specification and validates Applicants asserted utility of hSLAP-2. Applicants assert that hSLAP-2 has a well-established utility and that the utility requirement has been met by the specification as originally filed, and as supported by the subsequent teachings of Holland et al, Pandey et al, and Loreto et al.

The Examiner also alleges that "Holland et al., (J. Exp. Med. 2001, Vol.14, 1263-1276) teach that although SLAP-2 and SLAP share structural homologies their mechanisms of action is different and further studies are required to determine the role and function of SLAP-2 protein".

Applicants disagree and believe the Examiners allegation is out of context and is not in-line with the teachings of Holland et al nor Pandey et al nor Loreto et al. Applicants do not refute that hSLAP-2 and SLAP have slightly different mechanisms of action despite their significantly shared homology. The latter is to be expected based upon the fact that SLAP-2 and SLAP are independent and distinct molecules that share overlapping functions. Applicants believe the Examiners comment is out of context since Holland et al and Pandey et al and Loreto et al each teach that hSLAP-2 has overlapping functions with SLAP. Holland et al comments throughout the manuscript on the overlapping role of hSLAP-2 with SLAP noting "SLAP-2 and SLAP may play a similar role in antigen receptor signaling" (see page 1274 and throughout the manuscript). Pandey et al also comments on the overlapping roles of hSLAP-2 and SLAP throughout their manuscript and take the overlapping functions one step further by noting "Since both SLAP and SLAP-2 are coexpressed in thymus, spleen, and lymph node, it is possible that they may have at least partially redundant roles in T cell signaling...therefore SLAP and SLAP-2 represent a family of proteins that may have partially overlapping functions" (see page 19137 and throughout the manuscript). Loreto et al also comments on the overlapping roles of hSLAP-2 and SLAP throughout their manuscript and note "The similarity that exists between the SH3 and SH2 protein interaction modules in SLAP-2 and SLAP suggests that these proteins might associate with a similar set of proteins...We propose that SLAP-2

and the related protein SLAP act in concert...to down-regulate signaling by promoting the lysomomal targeting and degradation of activated antigen receptor complexes (see page 4250, 4253 and 4254). Applicants point out to the Examiner that the patent laws only require that the claimed invention be complete and meet the statutory requirements for patentability. While some of the teachings of Holland et al Pandey et al and Loreto et al suggests SLAP-2 has a slightly different mechanism of action than its close homolog SLAP, their teachings do not detract from Applicants disclosure, but rather support the function and utility of hSLAP-2 as originally conceived by Applicants inventors. The fact that hSLAP-2 may have a slightly different mechanism suggests that it may have other functions and utilities that are distinct from the functions and utilities of SLAP. As pointed out above, the latter is expected since hSLAP-2 is not the same molecule as SLAP. Applicants assert that the claimed hSLAP-2 polynucleotide inventions are complete and no additional research is required. Applicants also assert that the claimed hSLAP-2 polynucleotides have a well-established utility based upon the teachings of Applicants specification which is supported by the subsequent teachings of Holland et al, Pandey et al, and Loreto et al.

b. The Examiner alleges "that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). Attwood *et al.* (Science, 2000,290,471-473) teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable. Given the above information, and in light of the art recognized fact that minor sequence differences can significantly affect a protein's function, one skilled in the art would find it more likely than not that h SLAP-2 of SEQ ID NO:2 is not having the same function as human SLAP. Thus, the homology-based assignment h SLAP-2 of SEQ ID NO:2 as human SLAP receptor does not appear to provide evidence of a specific and substantial utility based on the knowledge of the skilled artisan and the data presented in the instant specification."

Applicants do not refute the statements presented by Attwood and Skolnick et al. However, even Attwood acknowledges that function can be predicted based upon the presence of motifs that

are essential for a particular function, stating "Gene family databases allow more specific functional diagnoses to be made than is possible by pairwise searching. They are based on the principle that related sequences can be aligned to find regions (motifs) that show little variation. These motifs usually reflect some vital structural or functional role...and they can be used to derive diagnostic family signatures." (see page 472 under "Function prediction through pattern recognition" section). The latter is also supported by the teachings of Kelly et al, Tomlinson et al, and Myung et al specifically related to SH2 and SH2/SH3 domains, and in particular adaptor proteins containing such domains as discussed *supra*. Importantly, the latter is also supported by the teachings of Applicants specification considering Applicants were able to successfully predict the physiological function of hSLAP-2 based upon its structural characteristics, the presence of the SH2 and SH2/SH3 domains, and its immune restricted expression pattern, among others. Moreover, the latter is also supported by the subsequent teachings of Holland et al, Pandey et al, and Loreto et al as they relate to hSLAP-2.

Re: Skolnick et al, Applicants do not refute that occasional assignment errors may occur when applying only homology comparisons to functional assignments. However, the lessons taught by Skolnick et al are not applicable to the instant case due to the convincing structural conservation of hSLAP-2 with other adaptor proteins, particularly SLAP, the homology to other adaptor protein family members, the presence of the SH2 and SH2/SH3 domains, and the immune restricted expression profile, particularly in peripheral blood lymphocytes, Jurkat T-cells and bone-marrow cells, which is further supported by the subsequent teachings of Holland et al, Pandey et al, and Loreto et al. As evidenced by the teachings of the instant specification, exceptions to Skolnick et al clearly exist. Applicants also assert that hSLAP-2 does have a specific, substantial, credible, and well-established utility based upon the arguments presented *supra*.

c. The Examiner also alleges that "There is no specific disease or specific function that is suggested by this limited homology. There is therefore no specific or substantial, utility that is well-known, apparent, or implied by the relationship of the instant polynucleotide to the polynucleotide encoding by human SLAP or mouse SLAP."

Applicants disagree with the Examiners allegations and point out to the Examiner that Applicants specification does, in fact, teach the physiological function of the hSLAP-2 polynucleotide as discussed *supra*. Applicants also do not agree with the Examiners allegation that the homology between hSLAP-2 and SLAP is limited. As Applicants have pointed out, the

homology between hSLAP-2 and SLAP is significant both from a sequence perspective (e.g., percent identity), as well as a structural perspective (e.g., conservation of SH2 and SH2/SH3 domains important for Src-like adaptor protein function). Applicants assert that hSLAP-2 does have a specific, substantial, credible, and well-established utility which is supported by the subsequent teachings of Holland et al, Pandey et al, and Loreto et al.

d. The Examiner also alleges that "A utility such as chromosome localization would apply to virtually every naturally occurring polynucleotide and is therefore not specific. Likewise, tissue-specific expression does not rely on specific properties or functions of the encoded protein. Each nucleic acid sequence that is expressed within a multicellular organism is expressed in some cell type and this expression is regulated in either a temporal or spatial manner. That, is, each expressed sequence is expressed in some cell type at some point in a hosts lifetime. Some transcripts are expressed embryonically, others are expressed only in particular cells, while still others are expressed in a wide variety of cells. In addition, some transcripts which are expressed in particular cells are only expressed in response to certain metabolic or environmental stimuli. Therefore, mere expression does not appear to provide evidence of a specific and substantial utility based on the knowledge of the skilled artisan and the data presented in the instant specification."

Applicants disagree and point out to the Examiner that Applicants specification does not teach the chromosome location of hSLAP-2. As a result, the Examiners utility allegation specific to chromosome localization does not apply to the claimed invention. Applicants also disgree with the Examiners allegation regarding tissue expression profiles. Although Applicants do not refute that expression profiling data, by itself, does not always provide evidence for specific and substantial utility, it is important to point out to the Examiner that such data does provide significant supporting evidence for specific and substantial utility when it is used in conjunction with other characteristics of the protein such as sequence homology, structural homology, the presence of conserved domains, etc. As Applicants have pointed out to the Examiner *supra*, the utility of hSLAP-2 was not based solely on its expression pattern, but rather on its significant homology to known adaptor proteins, particularly SLAP family members, the presence of the conserved SH2 and SH2/SH3 domains, in ***conjunction*** with its shared expression profile to other SLAP family members. Applicants assert that hSLAP-2 does have a specific, substantial, credible, and well-established utility which is supported by the teachings of Applicants specification and the subsequent teachings of Holland et al, Pandey et al, and Loreto et al.

e. The Examiner also alleges that "...the specification does not disclose any diseases or conditions known to be associated with the hSLAP polypeptide, encoded by SEQ ID NO:2 or any conditions associated with altered levels (increase or decrease) of said polypeptide. Since any protein may potentially be used as a treatment agent, this utility would not be considered to be specific. Since no particular disease or condition is disclosed, the artisan would have been required to perform additional experimentation to identify and/or reasonably confirm the asserted use of hSLAP polypeptide as a treatment agent and therefore, this utility would not be considered to be substantial. Therefore, identification of hSLAP polypeptide, encoded by SEQ ID NO:2 or nucleic acid of SEQ ID NO: I, encoding said polypeptide would not be sufficient to identify or confirm a "real world" context of use; clearly further research would be required to identify a disease in which the encoded protein is involved that can be treated using said a protein or nucleic acid encoding said protein."

Applicants disagree with the Examiners allegation and point out that the patent laws do not require the disclosure of any diseases or conditions known to be associated with a particular molecule in order to meet the utility requirement. Rather, the patent laws only require that an asserted utility be specific and substantial or represent a well-established utility. Polynucleotides and polypeptides may have a number of utilities that meet these requirements that are independent of any disease or disorder. As Applicants have pointed out *supra*, the teachings of the instant specification convincingly demonstrate that hSLAP-2 has a specific and substantial utility as well as a well-established utility as supported by the subsequent teachings of Holland et al, Pandey et al, and Loreto et al. Since Applicants have convincingly demonstrated that hSLAP-2 is a Src-like adaptor protein, and correctly predicted the physiological function of hSLAP-2 based upon its sequence and structural homology to SLAP in conjunction with its shared expression pattern with SLAP, Applicants assert that one skilled in the art would recognize that hSLAP-2 would be useful as a target for therapeutic intervention of any disease or condition that is associated with SLAP. The role of SLAP as a negative regulator of T-cell receptor signaling was well known, and well-established, prior to Applicants filing date (see Tang et al., PNAS 96:9775-9780 (1999); and Sosinowski et al., J. Exp. Med., 191(3):463-473 (2000); submitted concurrently herewith). Disorders affecting T-cell antigen receptor signaling were also well known prior to Applicants filing date, and include for Example, T-cell tumors, lymphomas, leukemias, thymomas, and autoimmune disorders, among others. Applicants assert that one skilled in the art would readily appreciate that hSLAP-2 has a specific, substantial, credible, and well-established utility based upon the teachings of Applicants

specification and the known association between SLAP and T-cell receptor signaling, which is all supported by the subsequent teachings of Holland et al, Pandey et al, and Loreto et al.

At a minimum, Applicants assert that one skilled in the art recognized prior to Applicants filing date that any molecule that binds to ZAP-70 would be expected to affect T-cell receptor signaling and thus would be useful as a target for therapeutic intervention for disorders affecting T-cell antigen receptor signaling, such as T-cell tumors, lymphomas, leukemias, thymomas, and autoimmune disorders, among others (see Chen et al., Cell 71:649-662 (1992); and Zhang et al., Cell 92:83-92 (1998); submitted concurrently herewith). Such disorders represent "real world" utility since they are real disorders afflicting the world today. The latter is supported by the fact that ZAP-70 links the activated T-cell receptor to downstream signaling events that ultimately leads to the transcription of genes such as IL-2, which is a hallmark of T-cell activation (Chan et al., EMBO J. 14:2499-2508 (1995); Williams et al., J. Biol. Chem. 271:19641-19644 (1996); and Williams et al., Mol. Cell. Biol., 18:1388-1399 (1998); submitted concurrently herewith). As demonstrated by Sosinowski et al, SLAP associates with ZAP-70. As pointed out *supra*, Applicants also conceived that hSLAP-2 is capable of binding to ZAP-70. The latter is also supported by the subsequent teachings of Holland et al, Pandey et al, and Loreto et al. Clearly, the skilled artisan would appreciate that no additional research would be required to identify a "real world" utility for hSLAP-2. Applicants reaffirm that the instant specification as originally filed supports the claimed hSLAP-2 polynucleotides as having a specific, substantial, credible and well-established utility. Applicants believe the Examiners rejection of Claims 21 to 40 have been overcome in light of Applicants arguments *supra*.

Applicants do not agree with the Examiners alleged application of Brenner v. Manson to the pending claims of the instant application. At issue in Brenner was whether a chemical process for synthesizing chemical compounds was patentable for an application that did not disclose any utility for the disclosed compounds (i.e., the patent application at issue in Brenner did not even describe the utility of the class of compounds that were orthologous to the claimed compounds at issue in the case either explicitly or through reference to a publication). Applicants assert that the instant patent application explicitly discloses the utility of the hSLAP-2 polynucleotide and polypeptides, in addition to any modulators thereof, as originally filed. Thus, since the utility of hSLAP-2 is already disclosed in the specification, Brenner v. Manson cannot apply.

IV. Rejections under 35 U.S.C. § 112, first paragraph

a. The Examiner has rejected Claims 21-40 under 35 U.S.C. § 112, first paragraph, alleging that the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility and that one skilled in the art clearly would not know how to use the claimed invention.

Applicants disagree. Applicants believe the Examiners allegations have been overcome in light of the arguments presented above, the teachings of Applicants specification, in addition to the subsequent teachings of Holland et al, Pandey et al, and Loreto et al. Since hSLAP-2 has a specific, substantial, and well established utility in the specification as originally filed, one skilled in the art clearly would know how to use the claimed invention. In addition, Applicants also assert that since the hSLAP-2 function and its biological significance are disclosed in the specification as originally filed, Applicants specification provides the requisite teachings that a skilled artisan would require to use the claimed invention.

V. Rejections under 35 U.S.C. § 112, first paragraph

a. The Examiner has rejected Claims 21, and 26 to 40 under 35 U.S.C. § 112, first paragraph, alleging that they contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention. More particularly, the Examiner alleges "[t]he specification does not reasonably provide enablement for: (i) *any* isolated nucleic acid molecule, comprising a polynucleotide sequence selected from the group recited in claim 21 (c- h), claimed in claims 21 (c-h) 26 and 28 -32; or (ii) *any* isolated nucleic acid molecule, comprises nucleotide 694 to 942 of SEQ ID NO: 1, claimed in claim 27; or (iii) *any* recombinant vector comprising any polynucleotide sequence selected from the group recited in claim 21 (c- h), or any recombinant host cells comprising said vectors, or a method of making any isolated polypeptide, comprising culturing said recombinant host cells claimed in claims 33, 34 and 35 accordingly; or (iv) *any* isolated polynucleotide of claim 21 wherein said nucleotide sequence further comprises a heterologous nucleic acid sequence, claimed in Claims 36 and 37; or (v) *any* isolated nucleic acid molecule comprising a polypeptide having a nucleotide sequence at least 85% identical to a sequence provided in claim 21, claimed in claim 38 or further comprising a heterologous nucleic acid sequence, claimed in Claim 39 and 40".

Applicants disagree with the Examiners allegation and assert that the instant specification does provide an enabling description for how to make an isolated nucleic acid which comprises an isolated polynucleotide encoding a polypeptide corresponding to amino acids 35 to 90 of SEQ ID NO:2 (Claim 21(c)); an isolated polynucleotide which comprises an isolated polynucleotide encoding a polypeptide corresponding to amino acids 94 to 176 of SEQ ID NO:2 (Claim 21(d)); an isolated polynucleotide which comprises an isolated polynucleotide encoding at least 100 contiguous amino acids of SEQ ID NO:2 (Claim 21(d)); an isolated polynucleotide degenerate from SEQ ID NO:1 as a result of the genetic code redundancy (Claim 21(f)); an isolated polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a) – (g); and any isolated nucleic acid molecule comprising a polypeptide having a nucleotide sequence at last 85% identical to a sequence provided in Claim 21. However, in an effort to facilitate prosecution, Applicants have amended Claim 21 to delete Claim 21(c), (d), (e), (f), and (h). Applicants have also canceled Claims 26, 27, 28, 29, 30, 32, 38, 39, and 40. Applicants believe the Examiners rejection of these Claims has been rendered moot in light of these amendments. Since Claims 33, 34, 35, 36 and 37 depend from Claim 21, the Examiners rejection of these claims as they relate to Claim 21(c), (d), (e), (f), and (h) has also been rendered moot.

Applicants have also amended Claim 21(g) to delete the "or fragment thereof" limitation in order to facilitate prosecution. Applicants believe the Examiners rejection of Claim 21(g) has been rendered moot in light of this amendment. Since Claims 31 depends from Claim 21(g), the Examiners rejection of Claim 31 has also been overcome. Since Claims 33, 34, 35, 36 and 37 also depend from Claim 21(g), the Examiners rejection of these claims as they relate to Claim 21(g) has also been rendered moot.

Applicants also disagree with the Examiners allegation specific to Claim 21(g) and assert that the instant specification does provide an enabling description for how to make an isolated nucleic acid that represents the complimentary sequence of a nucleic acid of Claim 21. As the Examiner will appreciate, the claimed polynucleotides are double stranded with the top strand, also referred to as the sense strand, serving as the coding strand for the hSLAP-2 sequences. The complimentary sequence of a sequence is simply its antisense, or complimentary strand, of the sense strand. Thus, a skilled artisan would only need to know the sense strand of a particular sequence to identify the complimentary sequence. Once that complimentary sequence is known, one skilled in the art would only need to synthesize the sequence using methods well known in the art. Methods for making complimentary sequences for polynucleotide sequences are well-known in the art (see Stein et al.,

Nucl. Acids Res., 16:3209 (1988); and Okano, Neurochem., 56:560 (1991); submitted concurrently herewith). Moreover, Applicants specification provides detailed teachings on how one skilled in the art could make and use complimentary sequences of the present invention (see paragraph numbers 133 to 146, and Example 4, for example). Applicants attribute the Examiners rejection to Claim 21(g) primarily to the "or fragment thereof" limitation. In the interest of facilitating prosecution, Applicants have amended Claim 21(g) to delete the "or fragment thereof" limitation. Applicants believe the Examiner's rejection has been rendered moot in light of this amendment. Since Claim 31 depends from Claim 21(g), the Examiners rejection of Claim 31 has also been rendered moot. Moreover, since Claims 33, 34, 35, 36 and 37 depend from Claim 21, the Examiners rejection of these claims as they relate to Claim 21(g) has also been rendered moot.

Applicants also assert that the Examiners rejections specific to the application of In re Wands, essential vs non-essential sequences, genus claims, application of Attwood and Ngo et al, hybridization, unpredictability, and undue experimentation have also been rendered moot in light of Applicants amendments described herein.

Applicants also assert that the Examiners allegation specific to the heterologous polypeptides claimed in Claims 36 and 37 and Claims 39 and 40 have also been rendered moot in light of Applicants amendments. Applicants attribute the Examiners rejection of Claims 36 and 37 to Claims 21(c - h). Since Claims 21(c), (d), (e), (f), and (h) have been deleted, Applicants believe the Examiners rejection of Claims 36 and 37 has been rendered moot. Moreover, Applicants cancelled Claims 39 and 40. Thus, the Examiners rejection of Claims 39 and 40 has also been rendered moot.

VI. Rejections under 35 U.S.C. § 112, first paragraph

a. The Examiner has rejected Claims 21 and 26 to 40 under 35 U.S.C. § 112, first paragraph, alleging as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. More particularly, the Examiner alleges "Applicant is not in possession of: (i) *any* isolated nucleic acid molecule, comprising a polynucleotide sequence selected from the group recited in claim 21 (c-h), claimed in claims 21 (c-h) 26 and 28 -32; or (ii) *any* isolated nucleic acid molecule, comprises nucleotide 694 to 942 of SEQ ID NO:1, claimed in claim 27; or (iii) *any* recombinant vector comprising any polynucleotide sequence selected from the group recited in claim 21 (c-h), or any recombinant host cells comprising said vectors, or a method of making any isolated polypeptide, comprising culturing said recombinant host

cells claimed in claims 33, 34 and 35 accordingly; or (iv) *any* isolated polynucleotide of claim 21 wherein said nucleotide sequence further comprises a heterologous nucleic acid sequence, claimed in Claims 36 and 37; or (v) *any* isolated nucleic acid molecule comprising a polypeptide having a nucleotide sequence at least 85% identical to a sequence provided in claim 21, claimed in claim 38 or further comprising a heterologous nucleic acid sequenced, claimed in Claim 39 and 40."

Applicants disagree with the Examiners allegation and assert that the instant specification provides an adequate description to demonstrate that Applicants were in possession of an isolated nucleic acid which comprises an isolated polynucleotide encoding a polypeptide corresponding to amino acids 35 to 90 of SEQ ID NO:2 (Claim 21(c)); an isolated polynucleotide which comprises an isolated polynucleotide encoding a polypeptide corresponding to amino acids 94 to 176 of SEQ ID NO:2 (Claim 21(d)); an isolated polynucleotide which comprises an isolated polynucleotide encoding at least 100 contiguous amino acids of SEQ ID NO:2 (Claim 21(d)); an isolated polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a) – (g); and any isolated nucleic acid molecule comprising a polypeptide having a nucleotide sequence at last 85% identical to a sequence provided in Claim 21. However, in an effort to facilitate prosecution, Applicants have amended Claim 21 to delete Claim 21(c), (d), (e), (f), and (h). Applicants have also canceled Claims 26, 27, 28, 29, 30, 32, 38, 39, and 40. Applicants believe the Examiners rejection of these Claims has been rendered moot in light of these amendments. Since Claims 33, 34, 35, 36 and 37 depend from Claim 21, the Examiners rejection of these claims as they relate to Claim 21(c), (d), (e), (f), and (h) has also been rendered moot.

Applicants have also amended Claim 21(g) to delete the "or fragment thereof" limitation in order to facilitate prosecution. Applicants believe the Examiners rejection of Claim 21(g) has been rendered moot in light of this amendment. Since Claims 31 depends from Claim 21(g), the Examiners rejection of Claim 31 has also been overcome. Since Claims 33, 34, 35, 36 and 37 also depend from Claim 21(g), the Examiners rejection of these claims as they relate to Claim 21(g) has also been rendered moot.

Applicants also disagree with the Examiners allegation specific to Claim 21(g) and assert that the instant specification does provide an adequate description to demonstrate that Applicants were in possession of the complimentary sequence of a nucleic acid of Claim 21. As the Examiner will appreciate, the claimed polynucleotides are double stranded with the top strand, also referred to as the sense strand, serving as the coding strand for the hSLAP-2 fragments. The complimentary sequence of a sequence is simply its antisense, or complimentary strand, of the sense strand. Thus, a

skilled artisan would only need to know the sense strand of a particular sequence to identify the complimentary sequence. Applicants specification teaches that the polynucleotides of the present invention can be double or single stranded (see paragraph number 38). Any double stranded polynucleotide having the same sequence as Applicants claimed polynucleotides would necessarily include the complimentary, or antisense, strand due to the complimentarity of nucleotide base pairs. Applicants adamantly assert that Applicants were in possession of the claimed complimentary sequences at the time of the filing of the instant specification. Applicants attribute the Examiners rejection to Claim 21(g) primarily to the "or fragment thereof" limitation. In the interest of facilitating prosecution, Applicants have amended Claim 21(g) to delete the "or fragment thereof" limitation. Applicants believe the Examiner's rejection has been rendered moot in light of this amendment. Applicants reserve the right to prosecute this claim in its original form in related applications. Since Claim 31 depends from Claim 21(g), the Examiners rejection of Claim 31 has also been rendered moot. Moreover, since Claims 33, 34, 35, 36 and 37 depend from Claim 21, the Examiners rejection of these claims as they relate to Claim 21(g) has also been rendered moot.

Applicants also assert that the Examiners rejections specific to genus claims (e.g., Fiers vs Revell; University of California v. Eli Lilly and Co.; and Vas-Cath Inc. v. Mahurkar) has also been rendered moot in consideration of Applicants amendments *supra*.

VII. Rejections under 35 U.S.C. § 112, second paragraph

a. The Examiner has rejected Claims 21 and 32 to 40 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More particularly, the Examiner has rejected Claim 21(h) as being "indefinite in the recitation of "a polynucleotide capable of hybridizing under stringent conditions" because the metes and bounds of such conditions are ambiguous and unclear."

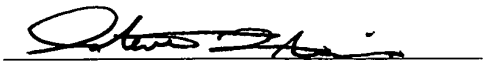
Applicants disagree. However, in the interest of facilitating prosecution, Applicants have deleted Claim 21(h), and cancelled Claims 32, and 38 to 40. Since Claims 33, 34, 35, 36, and 37 depend from Claim 21, Applicants believe the Examiner's rejection has been rendered moot in light of this amendment as it relates to Claim 21(h).

Applicants believe that all of the Examiners rejections and objections have been overcome and that all of the pending claims before the Examiner are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

Applicants reply is timely filed and no extensions of time are required.

If any fee is due in connection herewith not already accounted for, please charge such fee to Deposit Account No. 19-3880 of the undersigned. Furthermore, if any extension of time not already accounted for is required, such extension is hereby petitioned for, and it is requested that any fee due for said extension be charged to the above-stated Deposit Account.

Respectfully submitted,



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BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Bristol-Myers Squibb
Attn: Gena Whitney
Rt. 206 & Priceline Rd
Princeton, NJ 08648

Deposited on Behalf of: Bristol-Myers Squibb

Identification Reference by Depositor:
DNA cloned gene: hSLAP-2

Patent Deposit Designation
PTA-3873

The deposit was accompanied by: __ a scientific description _ a proposed taxonomic description indicated above.

The deposit was received November 20, 2001 by this International Depository Authority and has been accepted.

AT YOUR REQUEST: X We will inform you of requests for the strain for 30 years.

The strain will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strain, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strain.

If the culture should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace it with living culture of the same.

The strain will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the culture cited above was tested November 28, 2001. On that date, the culture was viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA.

Signature of person having authority to represent ATCC:

Date: December 18, 2001

Tanya Nunnally, Patent Specialist, Patent Depository

cc: Stephen B. Davis